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(54) Title: NEUROTROPHIC THIO SUBSTITUTED PYRIMIDINES

(57) Abstract

The present invention relates to a series of substituted thiopyrimidines, to pharmaceutical compositions which contain them, to methods for their preparation and to their use in therapy, particularly in the treatment of neurodegenerative or other neurological disorders of the central and peripheral systems.

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NEUROTROPHIC THIO SUBSTITUTED PYRIMIDINES

BACKGROUND OF THE INVENTION

The present invention relates to novel derivatives of a series of substituted pyrimidines, to pharmaceutical compositions which contain them, to methods for their preparation and to their use in therapy, particularly in the treatment of neurodegenerative or other neurological disorders of the central and peripheral systems including nerve injuries.

Dementing disorders such as age-related cognitive disorders, e.g., senility or Alzheimer's disease are medical conditions for which there are currently only limited therapies. Although studies suggest that multiple neurotransmitter systems are involved in senile dementia, a loss of cholinergic neurons and a severe depletion of choline acetyltransferase appear to show the earliest and strongest correlations with functional cognitive impairment [see P.T. Francis et al., Neurochemical Studies of Early-onset Alzheimer's Disease. N. Engl. J. Med., 313, 7 (1985); R.T. Bartus et al., The Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Directions. Ann. N. Y. Acad. Sci., 444, 332 (1985); F. Hefti and L.S. Schneider, Nerve Growth Factor and Alzheimer's Disease, Clin. Neuropharmacol., 14, S62 (1991)]. Several groups have attempted to stimulate cholinergic activity by blocking the breakdown of acetylcholine with acetylcholine esterase inhibitors or by introducing muscarinic or nicotinic agonists [see R.T. Bartus et al., The Cholinergic Hypothesis of Geriatric Memory Dysfunction. Science, 217, 408 (1982); J. Varghese et al., Chapter 21. Alzheimer's Disease: Current Therapeutic Approaches. Annu. Rep. Med. Chem., 28, 197 (1993)]. The approved drugs Cognex and Aricept are acetylcholine esterase inhibitors.

Nerve growth factor (NGF) is the best characterized neurotrophic factor that is capable of inducing cell differentiation of neural cells and promoting neurite sprouting. The neurotrophic protein NGF primarily affects

cholinergic neurons in the central nervous system and may be necessary for their survival [see F. Hefti and P.A. Lapchak, Pharmacology of Nerve Growth Factor in the Brain. Adv. Pharmacol., 24, 239 (1993)]. NGF is not systemically bioavailable, but if it is injected or infused directly into brain, it prevents neuronal cell loss and restores cognitive function in aged or lesioned rats or monkeys [see W. Fischer et al., NGF Improves Spatial Memory in Aged Rodents as a Function of Age. J. Neurosci.,11, 1889 (1991)]. NGF effects ultimately result in the stimulation of choline acetyltransferase, the enzyme for biosynthesis of acetylcholine and the promotion of neurite growth. Consequently, small molecules that produce neurotrophic or "nerve growth factor-like" (NGF-like) properties in mammalian cell cultures have potential for use in the treatment of dementing disorders such as age-related senility or Alzheimer's disease and other neurodegenerative conditions such as peripheral neuropathies, Parkinson's, stroke damage, transient ischemic attacks, trauma-head injuries or other nerve injuries.

There are several reports of small molecules that exhibit various aspects of NGF-like activity. Isaxonine [2-(isopropylamino)pyrimidine] was developed as a neurotrophic pharmaceutical but the clinical application was withdrawn, possibly due to toxicological effects [see S. Lehmann et al., Neurite Outgrowth of Neurons of Rat Dorsal Root Ganglia Induced by New Neurotrophic Substances with Guanidine Group. Neurosci. Lett., 152, 57 (1993)]. Several 2-(piperazino)pyrimidine derivatives were reported to possess NGF-like activity and are being studied further for use in treating CNS degenerative diseases [see A. Awaya et al., Neurotrophic Pyrimidine Heterocyclic Compounds. Biol. Pharm. Bull., 16, 248 (1993)]. AIT-082 (4[[3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl]amino]benzoic acid) is reported to enhance NGF action in cultured PC-12 cells and to restore age-induced working memory deficits in mice [see P.J.. Middlemiss et al., AIT-082, A Unique Purine Derivative, Enhances Nerve Growth Factor Mediated Neurite Outgrowth from PC-12 cells. Neuroscience Let., 199, 131 (1995)].

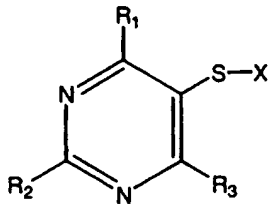
The compound SR57746A is reported to have nerve growth factor potentiating activity and is in clinical trials [see Fournier J, et al. Protective Effects of SR57746A in Central and Peripheral Models of Neurodegenerative Disorders in Rodents and Primates. Neuroscience, 55(3), 629-41, Aug 1993; US Patents 5,270,320 and 5,462,945]. In addition, EP0372934, EP0459819 and U.S. Patent 5,075,305 disclose substituted pyrimidines having NGF-like properties and its possible use in treating CNS degenerative diseases like Alzheimer's disease as well as peripheral neuropathies and other peripheral nervous system disorders.

SUMMARY OF THE INVENTION

We have now discovered a series of substituted pyrimidines that demonstrate NGF-like activity and/or enhancement of NGF activity in PC12 cells. The compounds stimulated both neurite outgrowth and choline acetyltransferase activity in *in vitro* experiments. Such activities are predictive for causing increased choline acetyltransferase activity in rat striatum and improving cognitative performance in animal models of age-induced working memory deficits by potentiating the activity of endogenous NGF in the brain. [see P.J.. Middlemiss et al., AIT-082, A Unique Purine Derivative, Enhances Nerve Growth Factor Mediated Neurite Outgrowth from PC-12 cells. Neuroscience Let., 199, 131 (1995); A.J. Glasky et al., Effect of AIT-082, a Purine Analog, on Working Memory in Normal and Aged Mice. Pharmacol. Biochem. Behav., 47, 325 (1994); R. Morris, Developments of a Water-maze Procedure for Studying Spatial Learning in the Rat. J. Neurosci. Methods, 11, 47 (1984)].

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there are provided novel compounds of Formula I:



Formula I

wherein

R_1 is NHR4, wherein R4 is C6-10 aryl, C2-10alkyl, (C1-6alkyl)j(C3-9cycloalkyl)(CH2)q or (C1-6alkyl)j(C6-10aryl)(CH2)q, wherein j is 0-2 and q is 0-6, or (C1-6alkyl)j(C4-9heterocycloalkyl)(CH2)q wherein j is 0-2, q is 0-6 and the heterocyclic ring contains one or more heteroatoms which may be the same or different and are O, S, N or NR' (wherein R' is hydrogen, C1-6 alkyl, hydroxyC2-6 alkyl, mercaptoC2-6alkyl, C1-6alkyloxyC2-6alkyl, C1-6alkylthioC2-6alkyl, C6-10arylcarbonyl, C1-7alkylcarbonyl, C1-7alkylsulfonyl or C6-10arylsulfonyl); or

R_1 is piperazino or homopiperazino wherein the 4-N is substituted with a carbonylR5 or sulfonylR5, wherein R5 is

H (excluding sulfonyl),
C1-10alkyl,
C3-10alkenyl,
C3-10alkynyl,
C1-6alkyloxy,
C1-6alkyloxyC1-6alkyl,
C1-6alkylthioC1-6alkyl,
C1-6alkylamino,

C6-10aryl(CH2)q wherein q is 0-6,
C6-10aryloxy(CH2)q wherein q is 0-6,
C6-10arylamino(CH2)q wherein q is 0-6,
(C1-6alkyl)j(C3-9cycloalkyl)(CH2)q wherein j is 0-2 and q is 0-6, or (C1-6alkyl)j(C4-9heterocycloalkyl)(CH2)q wherein j is 0-2, q is 0-6 and the heterocyclic ring contains one or more heteroatoms which may be the same or different and are O, S, N or NR', wherein R' is hydrogen, C1-6alkyl, hydroxyC2-6alkyl, mercaptoC2-6alkyl, C1-6alkyloxyC2-6alkyl, C1-6alkylthioC2-6alkyl, C6-10arylcarbonyl, C1-7alkylcarbonyl, C1-7alkylsulfonyl or C6-10arylsulfonyl,

and wherein C atoms of R4 and R5 may optionally be substituted with one or more substituents selected from the group consisting of

hydroxyl,
halogen,
thiol,
oxo,
thioxo,
carboxy,
carboxamide,
C1-7alkyl carbonyl,
C1-7alkyl thiocarbonyl,
C1-8alkyloxy,
C1-8alkylthio,
C1-8alkylsulfinyl,
C1-8alkylsulfonyl,
C1-5alkyloxyC1-5alkyl,
C1-5alkylthioC1-5alkyl,
C1-5alkylsulfinylC1-5alkyl, and
C1-5alkylsulfonylC1-5alkyl;

R_2 is H or NH2;

R_3 is H;

X is a C6-10 aryl ring optionally substituted with one or more substituents selected from the group consisting of

halogen,
hydroxyl,
C1-6alkyl,
hydroxyC1-6alkyl,
oxoC2-7alkyl,
C2-7alkenyl,
C2-7alkynyl,
C1-6alkoxy,
CF3,
CF3C1-6alkyl,
OCF3, and
CF3C1-6alkoxy;

or pharmaceutically acceptable esters, amides, esters, amides, salts or solvates thereof.

The present invention includes all enantiomeric and diastereomeric forms of the compounds of Formula I either individually or admixed in any proportion.

The present invention further includes prodrugs and active metabolites of the compounds of Formula I. A prodrug includes any compound which, when administered to a mammal, is converted in whole or in part to a compound of Formula I. An active metabolite is a physiologically active compound which results from the metabolism of a compound of Formula I, or a prodrug thereof, when such compound or prodrug is administered to a mammal.

The compounds of Formula I above and their pharmaceutically acceptable esters, amides, salts or solvates are sometimes hereinafter referred to as "the compounds according to the invention".

By "alkyl" is meant straight or branched chain alkyl. The alkyl groups may be optionally substituted with hydroxy, amino or halogen.

By "aryl" is meant an aromatic ring such as phenyl or naphthyl. The aryl groups may be optionally substituted with hydroxy, amino or halogen.

By "heteroaryl" is meant a ring containing 1 to 4 heteroatoms selected from the group consisting of N, O and S.

By "halogen" is meant F, Cl, Br or I.

Preferred compounds of Formula I are those wherein X is substituted phenyl; and pharmaceutically acceptable esters, amides, salts or solvates thereof.

Further preferred compounds of Formula I are those wherein R_1 is C1-10alkylcarbonylpiperizino, hydroxyC3-9cycloalkylamino, or hydroxyC6-10arylamino, and X is substituted phenyl, and pharmaceutically acceptable esters, amides, salts or solvates thereof.

Most preferred compounds of Formula I are those wherein R_1 is 4-acetylpiperazino, 4-oxocyclohexylamino, trans-4-hydroxycyclohexylamino, 4-hydroxyanilino, or 4-(2-hydroxyethylamino); X is phenyl optionally substituted with 4-chloro, 2,4 dichloro, 4- bromo, 2-fluoro-4-chloro, 2-chloro-4-fluoro, 2-methyl-4-chloro, 4-methyl, or 4-ethyl; and R_2 is NH2; and pharmaceutically acceptable esters, amides, salts or solvates thereof.

Specifically preferred compounds of Formula I are:

4-acetylpiperazino-2-amino-5-(4-chlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2,4-dichlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(4-bromophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2-fluoro-4-chlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2-chloro-4-fluorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2-methyl-4-chlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(4-methylphenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(4-ethylphenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-chlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-bromophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2-fluoro-4-chlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2-chloro-4-fluorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2-methyl-4-chlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-methylphenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-ethylphenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-chlorophenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-bromophenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2-fluoro-4-chlorophenylthio) pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2-chloro-4-fluorophenylthio) pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2-methyl-4-chlorophenylthio) pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-methylphenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-ethylphenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(4-chlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2,4-dichlorophenylthio)pyrimidine

2-amino-4- hydroxyanilino-5-(4-bromophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2-fluoro-4-chlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2-chloro-4-fluorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2-methyl-4-chlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(4-methylphenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(4-ethylphenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-chlorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-bromophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2-fluoro-4-chlorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2-chloro-4-fluorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2-methyl-4-chlorophenylthio)
pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-methylphenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-ethylphenylthio)pyrimidine
2-Amino-5-(2-chloro-4-ethylphenylthio)-4-(trans-4-hydroxycyclohexylamino)
pyrimidine
2-Amino-5-(2,6-dichlorophenylthio)-4-(trans-4-hydroxycyclohexylamino)
pyrimidine
2-Amino-5-(4-chloro-2-methylphenylthio)-4-
(trans-4-hydroxycyclohexylamino)pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-
(4-trifluoromethylphenylthio)pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(4-methylphenylthio)
pyrimidine
2-Amino-5-(4-chloro-2-fluorophenylthio)-4-
(trans-4-hydroxycyclohexylamino)pyrimidine
2-Amino-5-(4-chloro-2-methylphenylthio)-4-
(trans-4-hydroxycyclohexylamino)pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(4-methylphenylthio)
pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(phenylthio)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-3-hydroxycyclohexylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-2-hydroxycyclohexylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-4-hydroxycyclohexylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-3-hydroxycyclohexylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-2-hydroxycyclohexylamino) pyrimidine

2-Amino-5-(2,4-dichlorophenylthio)-4-(4-oxocyclohexylamino)pyrimidine

2-Amino-5-(2,4,6-trichlorophenylthio)-4-(4-oxocyclohexylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-4-(hydroxymethyl)cyclohexylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-3-(hydroxymethyl)cyclohexylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-4-(hydroxymethyl)cyclohexylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylmethylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-3-hydroxycyclopentylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-2-hydroxycyclopentylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-3-hydroxycyclopentylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-2-hydroxycyclopentylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-3-(hydroxymethyl)cyclopentylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-2-(hydroxymethyl) cyclopropylmethylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-2-(hydroxymethyl)
cyclopropylmethylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-
(1-hydroxycyclopropylmethylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-
(1-hydroxycyclopentylmethylamino)pyrimidine
2-Amino-5-(4-chlorophenythio)-4-(2-hydroxy-1-methyl(ethylamino))
pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(1-hydroxymethyl-ethylamino)pyrimidine
2-Amino-5-(4-chlorophenythio)-4-(1,1-dimethyl-2-hydroxy(ethylamino))
pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(1-hydroxymethyl-2-hydroxy(ethylamino))
pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2-hydroxy-1-hydroxymethyl-1-methyl
(ethylamino))pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(tris(hydroxymethyl)methylamino)
pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2,3-dihydroxypropylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(3,4-dihydroxybutylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2-methoxyethylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2-(2-hydroxyethylamino)ethylamino)
pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-((2-aminoethyl)(2-hydroxyethyl)amino)
pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2-hydroxyethylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-(2-hydroxyethyl)piperazinoamino)
pyrimidine
2-Amino-5-(2,4-dichlorophenylthio)-4-(4-(2-hydroxyethyl)piperazinoamino)
pyrimidine
2-Amino-5-(2-chloro-4-ethylphenylthio)-4-(4-acetylpiperazino)pyrimidine
2-Amino-5-(2,4-dichlorophenylthio)-4-(4-acetylpiperazino)pyrimidine
2-Amino-5-(2,6-dichlorophenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-5-(4-chloro-2-methylphenylthio)-4-(4-acetylpiperazino)pyrimidine
2-Amino-4-(4-acetylpiperazino)-5-(4-trifluoromethylphenylthio)pyrimidine
2-Amino-5-(2-chloro-4-fluorophenylthio)-4-(4-acetylpiperazino)pyrimidine
2-Amino-5-(4-chloro-2-methylphenylthio)-4-(4-acetylpiperazino)pyrimidine
2-Amino-4-(4-acetylpiperazino)-5-(4-methylphenylthio)pyrimidine
2-Amino-4-(4-acetylpiperazino)-5-(phenylthio)pyrimidine
5-(4-Chlorophenylthio)-4-(4-acetylpiperazino)pyrimidine;
5-(2,4-Dichlorophenylthio)-4-(4-acetylpiperazino)pyrimidine;
4-(4-Acetoxyanilino)-2-amino-5-(4-chlorophenylthio)pyrimidine
4-(4-Acetylhomopiperazino)-2-amino-5-(4-chlorophenylthio)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-[2-hydroxy-1-(R-ethyl)-ethylamino] pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-[[2-(morpholino)ethylamino]pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(1-morpholinoamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-hydroxyphenethylamino)pyrimidine
2-Amino-4-(trans-2-hydroxycyclohexylaminomethyl)-5-(4-chlorophenylthio) pyrimidine
2-Amino-4-(4-aminomethyl-N-acetylpiperidinyl)-5-(4-chlorophenylthio) pyrimidine
2-Amino-4-(1-hydroxy-1-aminomethylcyclohexyl)-5-(4-chlorophenylthio) pyrimidine
4-(4-trans-Acetoxycyclohexylamino)-2-amino-5-(4-chlorophenylthio) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-isobutryloxy-cyclohexylamino) pyrimidine
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2-Amino-5-(4-chlorophenylthio)-4-(4-trans-(4-chlorobenzoyloxy)-cyclohexylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-L-valyloxycyclohexylamino) pyrimidine
4-(4-Acetoxyphenylamino)-2-amino-5-(4-chlorophenylthio)pyrimidine
2-Amino-4-phenylamino-5-(4-chlorophenylthio)pyrimidine
2-Amino-4-(4-trans-hydroxycyclohexylamino)-5-(4-hydroxyphenylthio) pyrimidine
2-Amino-4-(acetamidophenylamino)-5-(4-chlorophenylthio)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(bis-hydroxymethylmethylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-hydroxy-3-nitro-anilino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(hydroxyamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(methoxyamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2-hydroxyethoxyamino)pyrimidine

or pharmaceutically acceptable esters, amides, salts or solvates thereof.

In one aspect of the invention there is provided the compounds according to the invention for use in medical therapy, particularly for the treatment of neurodegenerative or neurological disorders of the central or peripheral nervous systems.

Examples of nervous system disorders which may be treated in accordance with the invention include dementing disorders such as age-related senility, senile dementia or Age Related Mental Impairment (ARMI), cerebral ataxia, Parkinson's disease, Alzheimer's disease, peripheral neuropathy, cognitive disorders secondary to stroke or trauma and attention-deficit hyperactivity disorder. In addition, nerve injuries, for example, spinal cord injuries, that require neuroregeneration may also be treated in accordance with the invention.

In a further aspect of the present invention there is included:

a) A method for the treatment of neurodegenerative or neurological disorders of the central or peripheral nervous systems which comprises treating the subject e.g., a mammal, such as a human, with a therapeutically effective amount of a compound according to the invention.

b) Use of a compound according to the invention in the manufacture of a medicament for the treatment of any of the above-mentioned disorders.

Examples of pharmaceutically acceptable salts of the compounds according to the invention include acid addition salts. However, salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compounds of the invention.

Preferred salts include those formed from hydrochloric, hydrobromic, sulfuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, oxaloacetic, methanesulfonic, ethansulfonic, p-toluenesulfonic, benzenesulfonic and isethionic acids.

The compounds according to the invention and pharmaceutically acceptable esters, amides, salts or solvates thereof may be employed in combination with other therapeutic agents for the treatment of the above disorders. Examples of such further therapeutic agents include Cognex, Aricept and other agents (e.g., acetylcholine esterase inhibitors, muscarinic or nicotinic receptor agonists, MAO inhibitors) that are effective for the treatment of neurodegenerative or neurological disorders of the central or peripheral nervous systems. The component compounds of such combination therapy may be administered simultaneously in either separate or combined formulations, or at different times, e.g., sequentially such that a combined effect is achieved.

While it is possible for compounds according to the invention to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. The formulations of the present invention comprise a compound of Formula I, as above defined, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, transdermal, intradermal, intramuscular and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon, for example, the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well know in the art of pharmacy. All methods include the step of bringing into association a compound of Formula I or a pharmaceutically acceptable salt thereof (active ingredient) with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion, or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophillised) condition requiring only the addition of the sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis, as generally described in Pharmaceutical. Res., 3(6), 318 (1986).

Formulations for rectal administration may be presented as suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example, buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Tablets or other forms of presentation in discrete units may conveniently contain an amount of compound of the Formula I which is effective for each of the above-mentioned indications at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually between 10 mg to 250 mg.

For the above-mentioned conditions and disorders, the compounds of the Formula I are preferably administered orally or by injection (intraparenteral or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also

the route of administration is likely to vary depending on the condition and its severity.

For each of the above-mentioned indications the compounds of the Formula I may be administered orally. The dose range for adult humans is generally from about 10 to 4000 mg/day and preferably from about 100 to 1000 mg/day. It may be advantageous to administer an initial dose of 200 to 2000 mg the first day then a lower dose of 100 to 1000 mg on subsequent days.

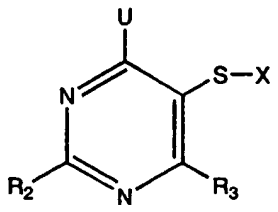
For each of the above-mentioned indications, the compounds according to the invention may be administered by injection at a dose of from about 1 to 2000 mg/day, and preferably from about 5 to 1000 mg/day.

The present invention further includes processes for the preparation of compounds of Formula I and esters, amides, salts or solvates thereof.

The compounds of Formula (I) and their esters, amides, salts and solvates may be prepared in accordance with the present invention by those methods hereinafter described, or in any manner known in the art for the preparation of compounds of analogous structure.

By way of illustration which does not limit the present invention, the compounds, esters, amides, salts and solvates of Formula (I) may be prepared by a process which comprises:

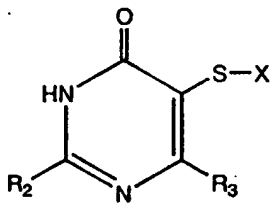
reacting a compound of Formula (II)



Formula II

wherein R_2, R_3 and X are as hereinbefore defined and U is a leaving group, with an amine NH2R4 wherein R4 is as hereinbefore defined, or with a monosubstituted piperazine. Suitable leaving groups include halogens such as chloride. The reaction is carried out in an organic solvent (e.g., ethanol, propanol) at a temperature of approximately 20°C to approximately 120°C. The compound of Formula (II) may be isolated and purified prior to reaction with the amine or may be used *in situ*.

Compounds of Formula (II) wherein U is a halogen atom can be prepared from compounds of Formula (III)

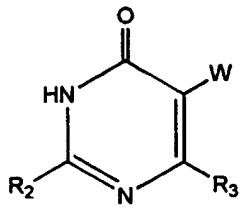


Formula III

wherein R_2, R_3 and X are as hereinbefore defined, by reaction with a halogenating agent (e.g., phosphorous oxychloride, phosphorous pentachloride, or a Vilsmeier reagent created using oxalyl chloride and N,N-diisopropylformamide) in a suitable organic solvent (e.g., dichloromethane, 1,2-dichloroethane, toluene, N,N-dimethlyformamide) at a

temperature of approximately 40°C to approximately 100° C.

Compounds of Formula (III) can be prepared from compounds of Formula (IV)

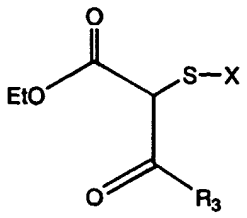


Formula IV

wherein R_2 and R_3 are as hereinbefore defined and W is a halogen atom such as bromo or chloro, by reaction with a suitable benzenethiol (e.g., 4-chlorobenzenethiol, 4-ethylbenzenethiol, 2,4-dichlorobenzenethiol) and a suitable base (e.g., potassium carbonate) in a suitable organic solvent (e.g., N,N-dimethylformamide, ethylene glycol, dimethylsulfoxide) at a temperature of 80°C to 140 °C.

Compounds of Formula (IV) can be prepared by various methods known in the art or are available from commercial sources.

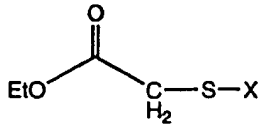
Alternatively, compounds of Formula (III) can be prepared from compounds of Formula (V)



Formula V

wherein R_3 and X are as hereinbefore defined, by reaction of an alkaline earth salt of Formula (V) with formamidine or guanidine in a suitable organic solvent (e.g., ethanol, methanol, 2-propanol, tert-butanol, tetrahydrofuran) at a temperature of approximately 60°C to the reflux temperature.

Compounds of Formula (V) can be prepared from compounds of Formula (VI)

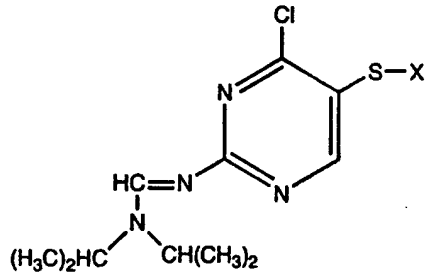


Formula VI

wherein X is as hereinbefore defined by reaction with an ester (e.g., ethyl formate) and a strong base (e.g., sodium hydride, potassium hydride, potassium tert-butoxide, sodium metal, lithium diisopropylamide) in a suitable organic solvent (e.g., tetrahydrofuran, ether, toluene) at a temperature of approximately 0°C to approximately 40°C.

Compounds of Formula (VI) can be prepared by various methods known in the art or are available from commercial sources.

Novel intermediates for the synthesis of compounds of Formula I are shown in Formula A:



Formula A

wherein X is as hereinbefore defined.

Specifically preferred intermediate compounds for synthesis of the above-listed specifically preferred compounds of Formula I are:

5-(phenylthio)isocytosine
5-(4-Methylphenylthio)isocytosine
5-(4-Chlorophenylthio)isocytosine
5-(4-Chloro-2-methylphenylthio)isocytosine
5-(4-Ethylphenylthio)isocytosine
5-(2-Chloro-4-fluorophenylthio)isocytosine
5-(2,4-Dichlorophenylthio)isocytosine
5-(4-Bromophenylthio)isocytosine
5-(2,4,6-trichlorophenylthio)isocytosine
5-(4-Trifluoromethylphenylthio)isocytosine
5-(4-Chlorophenylthio)-2-(diisopropylaminomethyleneamino)-4-chloropyrimidine
5-(2,4-Dichlorophenylthio)-2-(diisopropylaminomethyleneamino)-4-chloropyrimidine
5-(4-Chloro-2-fluorophenylthio)isocytosine, and
5-(2,6-Dichlorophenylthio)isocytosine.

Esters and amides of compounds of Formula I can be made by reaction with a carbonylating agent (e.g., ethyl formate, acetic anhydride, methoxyacetyl chloride, benzoyl chloride, methyl isocyanate, ethyl chloroformate, methanesulfonyl chloride) and a suitable base (e.g., 4-dimethylaminopyridine, pyridine, triethylamine, potassium carbonate) in a suitable organic solvent (e.g., tetrahydrofuran, acetone, methanol, pyridine, N,N-dimethylformamide) at a temperature of 0°C to 60° C.

Salts of the compounds of Formula I can be made from the free base form by reaction with the appropriate acid.

The following Examples illustrate the present invention but should not be construed as a limitation to the scope thereof.

Example 1

Preparation of 5-(4-chlorophenylthio)isocytosine

Isocytosine (100g, 0.90 mole) and glacial acetic (I L) were combined in a 2 L 3-neck round bottom flask equipped with an air stirrer, dropping funnel and thermometer. Neat bromine (154 g, 096 mole) was added portionwise over about 2.5 hours to the rapidly stirred suspension. After completion of the addition, the mixture was stirred overnight. The thick mass was vacuum filtered on an 18.5 cm Buchner funnel, washed with cold water (2 x 1L) to remove most of the bright yellow color, and resuspended in cold water with mechanical stirring. Concentrated ammonium hydroxide (about 75 mL) was added in portions until pH8 was sustained for at least 15 minutes. The mixture was filtered, the cake was washed with water and dried overnight in a vacuum oven at 120°C to give 5-bromoisocytosine as an off-white powder (78.6% yield).

4-Chlorobenzenethiol (18.8g, o.13mole) was melted with a heat gun and

weighed directly into a 500 mL 3-neck round bottom flask maintained under an argon atmosphere. The flask was then equipped with a magnetic stirrer and a reflux condenser vented to a scrubbing tower containing household bleach. Dimethylformamide (170 mL), 5-bromoisocytosine (19.0g, 0.10mole), and potassium carbonate (18g, 0.13mole) were added and the reaction mixture was placed in an oil bath preheated to approximately 110°C. The turbid brown solution was stirred for 4 hours at 104-114°C, cooled slightly and then poured onto ice (900 g) and water with stirring. The mixture was acidified with 6M HCl (25 mL) to pH 6, and the white solid was collected by vacuum filtration and washed with water. The damp cake was slurried with a mixture of diethyl ether (900 mL) and methanol (60 mL) for one hour. The solid was collected by filtration, washed with ether, and air dried to give 5-(4-chlorophenylthio)isocytosine as a white solid, mp 301-303°C, 21.6g (yield 85.0%).

Example 2

Preparation of 2-amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino)pyrimidine

N,N-diisopropylformamide (31.0 g, 0.24 mole) and methylene chloride (550 mL) were combined in a 2 L 3-neck round bottom flask equipped with an air stirrer, dropping funnel, and reflux condenser. The apparatus was flushed with argon, and oxalyl chloride (33.4 g, 0.26 mole) was placed in the dropping funnel. The oxalyl chloride was added portionwise over approximately 1.5 hours to the rapidly stirred solution. Stirring was continued for about 15 minutes after completion of the addition and then 5-(4-chlorophenylthio)isocytosine (21.6g, 0.085 mole)was added through a powder funnel. The mixture was brought to reflux and held for 1.5 - 2 hours until all solids dissolved. The mixture was cooled slightly, and excess Vilsmeier reagent was destroyed by the slow, portionwise addition of saturated aqueous $NaHCO_3$ solution (500 mL) to pH 7. The aqueous phase was largely removed by aspiration into a 2 L vacuum flask, and the

organic extract was washed with water (3 x 500 mL) and brine (1 x 500 mL). The remaining organic extract was poured into a 1 L separatory funnel for the final phase split; it was then dried (Na_2SO_4) and filtered through a silica gel bed (33 g, 2x 30 cm). The yellow filtrate was collected, and the bed was washed with additional CH_2Cl_2 until the washings were nearly colorless. The combined filtrates were stripped in vacuo to an amber oil, and hexanes (300 mL) were added to the warm oil with rapid magnetic stirring. Crystallization of the product began quickly. The mixture was allowed to cool with stirring, chilled in ice/water, and the solid was collected by filtration, washed with hexanes and air dried to give 5-[(4-chlorophenyl)thio]-2-(diisopropylaminomethyleneamino)-4-chloropyrimidine as a white powder, mp 110-111°C, yield 25.3 g (77.7%).

5-[(4-chlorophenyl)thio]-2-(diisopropylaminomethyleneamino)-4-chloropyrimidine (9.7g, 0.025 mole) and trans-4-aminocyclohexanol hydrochloride (15.16g, 0.100 mole)were combined in absolute ethanol (97 mL), and triethylamine (0.2 mole, 28 mL) was added. The mixture was then refluxed for 3 - 5 days. The mixture was cooled to approximately room temperature and concentrated HCl (10 mL) was added. The mixture was then heated at reflux for 1 - 1.5 hours, cooled and stripped in vacuo. The solid residue was slurried in water (100 mL), and the solid was collected by filtration, washed with water (1 x100 mL) and air-dried to give 2-amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino)pyrimidine as a white solid, mp 196-197°C, yield 8.16 g (93.0%).

Example 3

Preparation of 2-amino-5-(4-chlorophenylthio)-4-(2-hydroxyethylamino)pyrimidine

To 26 ml of a solution of 5-[(4-chlorophenyl)thio]-2-

(diisopropylaminomethyleneamino)-4-chloropyrimidine (5g, 0.130 mole) in dry ethanol was added ethanolamine (5g, 82 mmoles). The mixture was refluxed for 11 hrs. After cooling, 10 ml of concentrated hydrochloric acid was added, and this mixture was refluxed for 50 minutes and then spin evaporated at 60° C in vacuo. The resulting syrup was suspended in 400 ml of water and stirred with 100 ml of dichloromethane. Phases were separated and the aqueous phase was stirred again with 100 ml of dichloromethane. The pH was adjusted to 7 with 3N NaOH. A large precipitate formed in the organic phase. The aqueous phase was removed and the solids in the organic phase were collected by filtration and washed with dichloromethane. The crude product (1.35g) was suspended in 80 ml of ethanol, then heated to boiling, and filtered while hot. As the filtrate cooled, a cotton-like precipitate formed. The solids were collected by filtration, washed with ethanol, and dried in vacuo at 110° C for 15 hours. 1.05g (42% yield) of a white solid was obtained. mp. 200° C.

Example 4

Preparation of 4-(4-acetylpiperazino)-2-amino-5-(4-chlorophenylthio)pyrimidine

To diisopropylformamide (14.1g, 109 mmoles) dissolved in 240 ml of dichloromethane was slowly added oxalyl chloride (14.1g, 111mmoles) with stirring. Five minutes after the end of the addition, solid 5-(4-chlorophenylthio)isocytosine (10.1g, 40 mmoles) was added and washed in with 250 ml additional dichloromethane. The mixture was refluxed for 1 hour and 10 minutes. After cooling, it was poured into 450 ml of ice cold saturated NaHCO3. After separating the phases, this extraction was repeated on the organic layer. The organic layer was then washed with 500 ml of ice cold water and finally with 400 ml of brine. After drying over stirred Na2SO4 for 4 hours, the suspension was filtered, and the filtrate was applied to a Silica Gel 60 (230-400 mesh, EM Science Co.) column (4 x 7 cm) and eluted with dichloromethane. The strongly uv absorbing

fractions were pooled and spin evaporated in vacuo at 45° C to give the intermediate chloropyrimidine as a syrup (24g). After dissolving in 100 ml of dry ethanol, the final volume was 124 ml.

To 26 ml of this solution was added 1-acetylpiperazine (4.65g, 36 mmoles). The mixture was refluxed for 11 hrs. After cooling, 10 ml of concentrated hydrochloric acid was added, and this mixture was refluxed for 45 minutes. Upon cooling a precipitate had formed which was removed by filtration. The filtrate was then spin evaporated at 60° C in vacuo. The resulting syrup was suspended in 400 ml of water and stirred with 100 ml of dichloromethane. Phases were separated and the aqueous phase was stirred again with 100 ml of dichloromethane. The pH was adjusted to 7 with 3N NaOH. The organic phase was washed twice with 450 ml of water then with 200 ml of brine and dried over Na_2SO_4. After filtration, the dried organic phase was applied to a Silica Gel (230-400 mesh) column (4 x 6 cm). The product was eluted with ethyl acetate and spin evaporated at 60° C in vacuo. The resulting material was redissolved in 5 ml of hot ethyl acetate. Upon the addition of hexanes, a solid formed. The solvents were removed by decanting and the solids were suspended in 40 ml of diethyl ether and boiled with stirring. The solids were collected by filtration, washed with hexanes, and dried in vacuo at 105° C. 300 mg (10% yield) of white powder was obtained. mp 140-141 ° C.

Example 5

Preparation of 2-amino-5-(4-chlorophenylthio)-4-(4-hydroxyanilino)pyrimidine hydrochloride

Nitrogen was bubbled through a solution of 9g (23.5 mmol) 5-(4-chlorophenylthio)-2- (diisopropylaminomethyleneamino)-4-chloropyrimidine (see Example 2) in 200 mL of methanol for 10 minutes. Then 2.66 g of 4-aminophenol (24.4 mmol) was added and nitrogen bubbled through the

suspension for 5 minutes. The mixture was then tightly sealed and stirred until all in solution. After 2 days at 24°C, 50 ml of concentrated hydrochloric acid was added and the mixture refluxed for 100 minutes. After spin evaporation at 60°C, the solid was crystallized from hot ethanol and dried in vacuo at 105°C. 7.22 g (81%) of product as a pale yellow powder was obtained, mp 273-275°C.

Example 6

Preparation of 4-(4-acetoxyanilino)-2-amino-5-(4-chlorophenylthio)pyrimidine

1.25 g (3.28 mmole) of 2-amino-5-(4-chlorophenylthio)-4-(4-hydroxyanilino)pyrimidine hydrochloride (see Example 5) and 0.03g of 4-dimethylaminopyridine were dissolved in 3.9 g of dry N,N-dimethylformamide. 0.47 g acetic anhydride were added, and the container was sealed. After 2 days at 24°C, 100 mL of CH_2Cl_2 were added to the reaction mixture and stirred with 150 mL of cold saturated aqueous $NaHCO_3$. The organic layer was washed twice with 250 mL of water, then with 200 mL brine and dried over Na_2SO_4. After filtering off the salt, the filtrate was applied to a Silica Gel 60 column (2.5 x 6.5 cm) which had been preequilibrated with hexanes. Eluates were 50 mL hexanes, a mixture of 150 mL hexanes and 150 mL CH_2C_{l2}, and 500 mL CH_2Cl_2. Fractions with product, which was pure by TLC (EtOAc; Rf 0.6), were pooled and spin evaporated to a waxy solid. This solid was removed from the flash with the aid of hot hexanes, collected by filtration, and washed with hexanes. After drying in vacuo at 100°C for 16 hours, 0.19 g (15% yield) of a white powder was obtained, mp 178-180°C.

The following compounds were prepared by methods similar to those of the above indicated Examples:

Chemical Name	MP°C
2-amino-5-(4-chlorophenylthio)-4-(2-methoxyethylamino)pyrimidine	109
2-amino-5-(4-chlorophenylthio)-4-(2,3-dihydroxypropylamino) pyrimidine	158-159
2-amino-5-(4-chlorophenylthio)-4-(1-hydroxymethyl-ethylamino) pyrimidine	200-201
2-amino-5-(4-chlorophenylthio)-4-(1-dimethyl-2-hydroxyethylamino) pyrimidine	142-143
4-(4-Acetylhompiperazino)-2-amino-5-(4-chlorophenylthio)pyrimidine	105-106
2-Amino-5-(4-chlorophenylthio)-4-[2-hydroxy-1-(R[-]-ethyl)-ethylamino] pyrimidine	119-121
2-Amino-5-(4-chlorophenylthio)-4-[[2-(morpholino)ethylamino] pyrimidine	110-111
2-Amino-5-(4-chlorophenylthio)-4-(1-morpholinoamino) pyrimidine	160-162
2-Amino-5-(4-chlorophenylthio)-4-(4-hydroxyphenethylamino) pyrimidine	177-182
trans-2-[N-{2-Amino-5-(4-chlorophenylthio)}pyrimidin-4-yl]-aminomethylcyclohexanol	140-142
4-[N-{2-Amino-5-(4-chlorophenylthio)}pyrimidin-4-yl]-aminomethyl-N-acetylpiperidine	173-175
1--[N-{2-Amino-5-(4-chlorophenylthio)}pyrimidin-4-yl]-aminomethylcyclohexanol	226-227
4-(4-trans-Acetoxycyclohexylamino)-2-amino-5-(4-chlorophenylthio) pyrimidine	200-201
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-isobutryloxy-cyclohexylamino)pyrimidine	123-124
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-trimethylacetoxy-cyclohexylamino)pyrimidine	170-171
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-propionyloxy-cyclohexylamino)pyrimidine	150-152
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-benzoyloxyoxy-cyclohexylamino)pyrimidine	159-169

2-Amino-5-(4-chlorophenylthio)-4-(4-trans-(4-chlorobenzoyloxy)-cyclohexylamino)-pyrimidine	155-156
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-L-valyloxycyclohexylamino) pyrimidine	foam
4-(4-Acetoxyphenylamino)-2-amino-5-(4-chlorophenylthio)pyrimidine	178-180
2-Amino-4-phenylamino-5-(4-chlorophenylthio)pyrimidine	169-170
2-Amino-4-(4-trans-hydroxycyclohexylamino)-5-(4-hydroxyphenylthio) pyrimidine	below 100
2-Amino-4-(acetamidophenylamino)-5-(4-chlorophenylthio)pyrimidine	217-218
2-[N-{2-Amino-5-(4-chlorophenylthio)}pyrimidin-4-yl]-amino-1,3-propanediol	200-201
2-Amino-5-(4-chlorophenylthio)-4-(4-hydroxy-3-nitro-anilino)pyrimidine	235

The following Examples illustrate representative pharmaceutical compositions wherein the "Active Ingredient" may be any compound of Formula I or a pharmaceutically acceptable salt thereof.

Example A - Tablet Composition

	mg/tablet
(a) Active Ingredient	250
(b) Lactose B.P.	210
(c) Povidone B.P.	15
(d) Sodium Starch Glycollate	20
(e) Magnesium Stearate	5

The composition is prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Example B - Capsule Composition

A capsule composition is prepared by admixing the ingredients and filling into a two-part hard gelatin capsule.

	mg/capsule
(a) Active Ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2

Example C - Injectable Composition

(a) Active Ingredient	0.200 g
(b) Hydrochloric Acid Solution 0.1 M or Sodium Hydroxide Solution 0.1M to pH	4.0 to 7.0
(c) Sterile Water q.s. to	10 ml

The active ingredient is dissolved in most of the water (35° - 40° C) and the pH is adjusted to between 4.0 and 7.0. The batch is then made up to volume with sterile water and filtered through a sterile micropore filter into a sterile amber glass vial (type 1) and sealed with sterile closures and overseals.

The compounds of the invention were assayed for neurotrophic activity as follows:

A. Screen for NGF-like Activity:

Cultured PC12 cells (rat adrenal pheochromocytoma from ATCC) have receptors for NGF. Responses include promotion of neurite outgrowth and elevation of choline acetyltransferase(ChAT) (L.A. Greene and A.S. Tischler, Cell Neurobiol., 3, 373 (1982)).

The following assay is modified from that described in HL White and PW Scates, Neurochem. Res., 16, 63 (1991). PC12 cells were cultured at 37° C in RPMI supplemented with HEPES buffer, pH7.5 (to 10 mM), fetal bovine serum, horse serum, glutamine, penicillin, streptomycin and non-

essential amino acids. Cultures were split 1:3 every 3 to 4 days. Exponentially dividing cells were plated into fresh medium on collagen-coated 12-well plastic dishes (10^5 cells/well).

After allowing one day for cell attachment, the medium was replaced with low serum medium, with or without test compounds with each condition in triplicate. The medium may contain up to 0.2 % ethanol, which was used as a solvent for most compounds tested. Cells were examined for morphological changes using an Olympus IMT-2 inverted research microscope. After 3 days incubation with test compounds, medium was removed and replaced with 0.2 ml of lysis and ChAT assay mixture. The plates were incubated at 37° C for 2 hours and then placed into a freezer at -20° C.

Compounds are judged NGF-like in this primary screen if they (1) increase the activity of ChAT, (2) enhance NGF-stimulated neurite outgrowth or (3) potentiate or appear additive with the action of NGF itself.

B. Choline Acetyltransferase (ChAT) Assays:

The assay mixture contained 100 mM phosphate, pH7.4, 0.1% NP-40, 150 mM NaCl, 1.5 mM choline, 10 mM EDTA, 0.1 mM eserine, 0.1 mM acetyl-coenzyme A and about 0.5 uCi (40-70 Ci/mol) [14C]acetyl-coenzyme A in each ml of mixture. Thawed and lysed cell reaction mixtures were diluted to 1 ml with water and transferred to 7 ml scintillation vials containing 5 ml of extraction/scintillation fluid solution (50 mg triphenyl borate, 50 mg PPO, 20 mg POPOP per 100 ml of 20% acetonitrile/80% toluene) and vortexed for 10 seconds. After all diluted well contents were transferred and mixed, all the vials were vortexed again for 30 seconds, rotated for about 2 hours, and then vortexed once more. The vials were centrifuged at 3000 rpm ($r_{max.}$ =16 cm) for 15 minutes and then counted in a Beckman LS6500 scintillation counter. Background counts from reaction mixtures with extracts from

nonstimulated cells (no NGF and no test compound) were subtracted from reaction product counts before comparisons of ChAT activities were made.

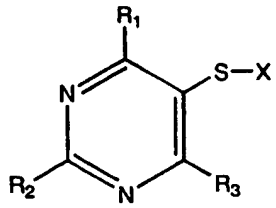
C. *In Vitro* Activity Data

The following data were obtained for representative compounds of the invention which (1) increased the activity of choline acetyltransferase (ChAT), (2) enhanced NGF-stimulated neurite outgrowth and/or (3) potentiated or appeared additive with the action of NGF itself. The concentration at which the test compound doubled the ChAT activity over the activity with NGF alone (no test compound) was recorded as the EC_{2x} value:

Compound of	EC_{2x} (uM)
Example 2	0.04
Example 3	0.35
Example 4	0.2
Example 5	0.07
Example 6	0.1

CLAIMS

1. A compound of the formula



wherein

R_1 is NHR4, wherein R4 is C6-10 aryl, C2-10alkyl, (C1-6alkyl)j(C3-9cycloalkyl)(CH2)q or (C1-6alkyl)j(C6-10aryl)(CH2)q, wherein j is 0-2 and q is 0-6, or (C1-6alkyl)j(C4-9heterocycloalkyl)(CH2)q wherein j is 0-2, q is 0-6 and the heterocyclic ring contains one or more heteroatoms which may be the same or different and are O, S, N or NR'
(wherein R' is hydrogen, C1-6 alkyl, hydroxyC2-6 alkyl, mercaptoC2-6alkyl, C1-6alkyloxyC2-6alkyl, C1-6alkylthioC2-6alkyl, C6-10arylcarbonyl, C1-7alkylcarbonyl, C1-7alkylsulfonyl or C6-10arylsulfonyl);
or

R_1 is piperazino or homopiperazino wherein the 4-N is substituted with a carbonylR5 or sulfonylR5, wherein R5 is

H (excluding sulfonyl),
C1-10alkyl,
C3-10alkenyl,
C3-10alkynyl,
C1-6alkyloxy,
C1-6alkyloxyC1-6alkyl,
C1-6alkylthioC1-6alkyl,
C1-6alkylamino,

C6-10aryl(CH2)q wherein q is 0-6,
C6-10aryloxy(CH2)q wherein q is 0-6,
C6-10arylamino(CH2)q wherein q is 0-6,
(C1-6alkyl)j(C3-9cycloalkyl)(CH2)q wherein j is 0-2 and q is 0-6,
or (C1-6alkyl)j(C4-9heterocycloalkyl)(CH2)q wherein j is 0-2, q is 0-6 and the heterocyclic ring contains one or more heteroatoms which may be the same or different and are O, S, N or NR', wherein R' is hydrogen, C1-6alkyl, hydroxyC2-6alkyl, mercaptoC2-6alkyl, C1-6alkyloxyC2-6alkyl, C1-6alkylthioC2-6alkyl, C6-10arylcarbonyl, C1-7alkylcarbonyl, C1-7alkylsulfonyl or C6-10arylsulfonyl,

and wherein C atoms of R4 and R5 may optionally be substituted with one or more substituents selected from the group consisting of

hydroxyl,
halogen,
thiol,
oxo,
thioxo,
carboxy,
carboxamide,
C1-7alkyl carbonyl,
C1-7alkyl thiocarbonyl,
C1-8alkyloxy,
C1-8alkylthio,
C1-8alkylsulfinyl,
C1-8alkylsulfonyl,
C1-5alkyloxyC1-5alkyl,
C1-5alkylthioC1-5alkyl,
C1-5alkylsulfinylC1-5alkyl, and
C1-5alkylsulfonylC1-5alkyl;

R_2 is H or NH2;

R_3 is H;

X is a C6-10 aryl ring optionally substituted with one or more substituents selected from the group consisting of

halogen,
hydroxyl,
C1-6alkyl,
hydroxyC1-6alkyl,
oxoC2-7alkyl,
C2-7alkenyl,
C2-7alkynyl,
C1-6alkoxy,
CF3,
CF3C1-6alkyl,
OCF3, and
CF3C1-6alkoxy;

or pharmaceutically acceptable esters, amides, esters, amides, salts or solvates thereof.

2. A compound of Claim 1 wherein X is substituted phenyl, and pharmaceutically acceptable esters, amides, salts or solvates thereof.

3. A compound of Claim 1 wherein R_1 is C1-10alkylcarbonylpiperizino, hydroxyC3-9cycloalkylamino, or hydroxyC6-10arylamino and X is substituted phenyl, and pharmaceutically acceptable esters, amides, salts or solvates thereof.

4. A compound of Claim 1 wherein R_1 is 4-acetylpiperazino, 4-oxocyclohexylamino, trans-4-hydroxycyclohexylamino, 4-hydroxyanilino, or 4-(2-hydroxyethylamino); X is phenyl optionally substituted with 4-chloro,

2,4 dichloro, 4- bromo, 2-fluoro-4-chloro, 2-chloro-4-fluoro, 2-methyl-4-chloro, 4-methyl, or 4-ethyl; and R_2 is NH2; and pharmaceutically acceptable esters, amides, salts or solvates thereof.

5. A compound selected from the group consisting of:
4-acetylpiperazino-2-amino-5-(4-chlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2,4-dichlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(4-bromophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2-fluoro-4-chlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2-chloro-4-fluorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(2-methyl-4-chlorophenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(4-methylphenylthio)pyrimidine
4-acetylpiperazino-2-amino-5-(4-ethylphenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-chlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-bromophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2-fluoro-4-chlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2-chloro-4-fluorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(2-methyl-4-chlorophenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-methylphenylthio)pyrimidine
2-amino-4-oxocyclohexylamino-5-(4-ethylphenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-chlorophenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-bromophenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2-fluoro-4-chlorophenylthio) pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2-chloro-4-fluorophenylthio) pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(2-methyl-4-chlorophenylthio) pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-methylphenylthio)pyrimidine
2-amino-4- hydroxycyclohexylamino-5-(4-ethylphenylthio)pyrimidine

2-amino-4- hydroxyanilino-5-(4-chlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(4-bromophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2-fluoro-4-chlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2-chloro-4-fluorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(2-methyl-4-chlorophenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(4-methylphenylthio)pyrimidine
2-amino-4- hydroxyanilino-5-(4-ethylphenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-chlorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2,4-dichlorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-bromophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2-fluoro-4-chlorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2-chloro-4-fluorophenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(2-methyl-4-chlorophenylthio)
pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-methylphenylthio)pyrimidine
2-amino-4-(2-hydroxyethylamino)-5-(4-ethylphenylthio)pyrimidine
2-Amino-5-(2-chloro-4-ethylphenylthio)-4-(trans-4-hydroxycyclohexylamino)
pyrimidine
2-Amino-5-(2,6-dichlorophenylthio)-4-(trans-4-hydroxycyclohexylamino)
pyrimidine
2-Amino-5-(4-chloro-2-methylphenylthio)-4-(trans-4-
hydroxycyclohexylamino)pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(4-
trifluoromethylphenylthio)pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(4-methylphenylthio)
pyrimidine
2-Amino-5-(4-chloro-2-fluorophenylthio)-4-(trans-4-
hydroxycyclohexylamino)pyrimidine
2-Amino-5-(4-chloro-2-methylphenylthio)-4-(trans-4-
hydroxycyclohexylamino)pyrimidine

2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(4-methylphenylthio) pyrimidine
2-Amino-4-(trans-4-hydroxycyclohexylamino)-5-(phenylthio)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-3-hydroxycyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-2-hydroxycyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(cis-4-hydroxycyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(cis-3-hydroxycyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(cis-2-hydroxycyclohexylamino) pyrimidine
2-Amino-5-(2,4-dichlorophenylthio)-4-(4-oxocyclohexylamino)pyrimidine
2-Amino-5-(2,4,6-trichlorophenylthio)-4-(4-oxocyclohexylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-4-(hydroxymethyl) cyclohexylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-3-(hydroxymethyl) cyclohexylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(cis-4-(hydroxymethyl)cyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylmethylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-3-hydroxycyclopentylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(trans-2-hydroxycyclopentylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(cis-3-hydroxycyclopentylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(cis-2-hydroxycyclopentylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-3-(hydroxymethyl) cyclopentylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(trans-2-(hydroxymethyl) cyclopropylmethylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(cis-2-(hydroxymethyl) cyclopropylmethylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(1-hydroxycyclopropylmethylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(1-hydroxycyclopentylmethylamino) pyrimidine

2-Amino-5-(4-chlorophenythio)-4-(2-hydroxy-1-methyl(ethylamino)) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(1-hydroxymethyl-ethylamino)pyrimidine

2-Amino-5-(4-chlorophenythio)-4-(1,1-dimethyl-2-hydroxy(ethylamino)) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(1-hydroxymethyl-2-hydroxy(ethylamino)) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(2-hydroxy-1-hydroxymethyl-1-methyl (ethylamino))pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(tris(hydroxymethyl)methylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(2,3-dihydroxypropylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(3,4-dihydroxybutylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(2-methoxyethylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(2-(2-hydroxyethylamino)ethylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-((2-aminoethyl)(2-hydroxyethyl)amino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(2-hydroxyethylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(4-(2-hydroxyethyl)piperazinoamino) pyrimidine

2-Amino-5-(2,4-dichlorophenylthio)-4-(4-(2-hydroxyethyl)piperazinoamino) pyrimidine

2-Amino-5-(2-chloro-4-ethylphenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-5-(2,4-dichlorophenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-5-(2,6-dichlorophenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-5-(4-chloro-2-methylphenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-4-(4-acetylpiperazino)-5-(4-trifluoromethylphenylthio)pyrimidine

2-Amino-5-(2-chloro-4-fluorophenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-5-(4-chloro-2-methylphenylthio)-4-(4-acetylpiperazino)pyrimidine

2-Amino-4-(4-acetylpiperazino)-5-(4-methylphenylthio)pyrimidine

2-Amino-4-(4-acetylpiperazino)-5-(phenylthio)pyrimidine

5-(4-Chlorophenylthio)-4-(4-acetylpiperazino)pyrimidine

5-(2,4-Dichlorophenylthio)-4-(4-acetylpiperazino)pyrimidine

4-(4-Acetoxyanilino)-2-amino-5-(4-chlorophenylthio)pyrimidine

4-(4-Acetylhomopiperazino)-2-amino-5-(4-chlorophenylthio)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-[2-hydroxy-1-(R-ethyl)-ethylamino] pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-[[2-(morpholino)ethylamino]pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(1-morpholinoamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(4-hydroxyphenethylamino)pyrimidine

2-Amino-4-(trans-2-hydroxycyclohexylaminomethyl)-5-(4-chlorophenylthio) pyrimidine

2-Amino-4-(4-aminomethyl-N-acetylpiperidinyl)-5-(4-chlorophenylthio) pyrimidine

2-Amino-4-(1-hydroxy-1-aminomethylcyclohexyl)-5-(4-chlorophenylthio) pyrimidine

4-(4-trans-Acetoxycyclohexylamino)-2-amino-5-(4-chlorophenylthio) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(4-trans-isobutryloxy-cyclohexylamino) pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(4-trans-trimethylacetoxy-cyclohexylamino)pyrimidine

2-Amino-5-(4-chlorophenylthio)-4-(4-trans-propionyloxy-cyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-benzoyloxy-cyclohexylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-(4-chlorobenzoyloxy)-cyclohexylamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-trans-L-valyloxycyclohexylamino) pyrimidine
4-(4-Acetoxyphenylamino)-2-amino-5-(4-chlorophenylthio)pyrimidine
2-Amino-4-phenylamino-5-(4-chlorophenylthio)pyrimidine
2-Amino-4-(4-trans-hydroxycyclohexylamino)-5-(4-hydroxyphenylthio) pyrimidine
2-Amino-4-(acetamidophenylamino)-5-(4-chlorophenylthio)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(bis-hydroxymethylmethylamino) pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(4-hydroxy-3-nitro-anilino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(hydroxyamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(methoxyamino)pyrimidine
2-Amino-5-(4-chlorophenylthio)-4-(2-hydroxyethoxyamino)pyrimidine
and pharmaceutically acceptable esters, amides, salts or solvates thereof.

6. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier therefor.

7. A pharmaceutical composition comprising a compound according to claim 5 and a pharmaceutically acceptable carrier therefor.

8. A method of treating a mammal having a neurodegenerative or neurological disorder of the central or peripheral nervous system with a therapeutically effective amount of a compound of claim 1.

9. A method of treating a mammal having a neurodegenerative or

neurological disorder of the central or peripheral nervous system with a therapeutically effective amount of a compound of claim 5.

10. A method according to claim 8 wherein the disorder is Alzheimer's disease.

11. A method according to claim 9 wherein the disorder is Alzheimer's disease.

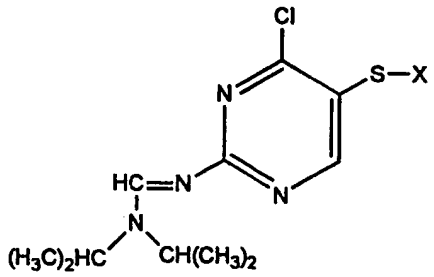
12. A method according to claim 8 wherein the disorder is peripheral neuropathy.

13. A method according to claim 9 wherein the disorder is peripheral neuropathy

14. A method according to claim 8 wherein the disorder is senile dementia.

15. A method according to claim 9 wherein the disorder is senile dementia

16. A compound of the formula



wherein X is a C6-10 aryl ring optionally substituted with one or more substituents selected from the group consisting of

halogen,
C1-6alkyl,
hydroxyC1-6alkyl,
oxoC2-7alkyl,
C2-7alkenyl,
C2-7alkynyl,
C1-6alkoxy,
CF3,
CF3C1-6alkyl,
OCF3, and
CF3C1-6alkoxy.

17. A compound selected from the group consisting of 5-(4-chlorophenylthio)-2-(diisopropylaminomethyleneamino)-4-chloropyrimidine and 5-(2,4-dichlorophenylthio)-2-(diisopropylaminomethyleneamino)-4-chloropyrimidine.

18. 2-Amino-5-(4-chlorophenylthio)-4-(trans-4-hydroxycyclohexylamino)pyrimidine.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/09004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/48 C07D239/46 A61K31/506 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 154 551 A (G.H. HITCHINGS) 27 October 1964 (1964-10-27) claims; examples 3,17,19; table I	1,2,6,7
A	EP 0 826 674 A (SUMITOMO) 4 March 1998 (1998-03-04) page 1 -page 11; tables	1,6-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2000	17/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...information on patent family members

Inter... nal Application No
PCT/US 00/09004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3154551 A	27-10-1964	GB 951431 A	
		GB 951432 A	
EP 826674 A	04-03-1998	CA 2217034 A	10-10-1996
		WO 9631488 A	10-10-1996
		JP 8333349 A	17-12-1996

SYNTHESIS AND ANTIINFLAMMATORY PROPERTIES OF o-CARBOXYPHENYLAMINO PYRIMIDINES

V. K. Karn, I. S. Tat'yanchenko,
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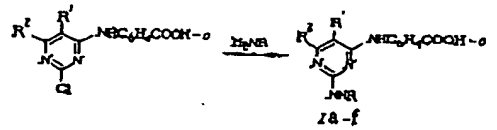
T. K. Ryabukha, and A. V. Vinnikova

UDC 616.281:547.853.3].012.1

Pyrimidine derivstives substituted with an o-carboxyphenylamino group at the 2, 4, or 5 position of the pyrmidine ring are physiologically active compounds [1-5].

The aim of the present work is to synthesize new o-carboxyphenylaminopyridines, with a phenylamino-, hydrazino-, or o-carboxyphenylamino group in the 2 position (Ia-f) and to study their antiinflammatory activity.



Ia:R = C_6H_5, $R^1 = R^2 = H$; Ib.R = NH_2, $R^1 = R^2 = H$;
Ic:R^1 = Br, $R^2 = CH_3$; Id:$R^1 = H$, $R^2 = COOH$;
Ie:$R^1 = H$, R_2 = Cl; If:$R^1 = H$, $R^2 = CH_3$;
Ig.f:R = C_6H_4COOH-o

Compounds Ia-f were obtained by the reaction of 2-chloro-4-(o-carboxyphenylamino) pyrimidines [6] with aniline, hydrazine, or anthranilic acid. The pyrmidines Ic-f were isolated as the hydrochlorides.

The 4-(o-carboxyphenylamino)pyrimidines Ia-f are yellow, crystalline substances, soluble in DMFA, DMSO, dilute acids, and bases; their properties are given in Table 1. The purity of compounds Ia-f were checked by TLC on UV 254 Silufol plates (ChSSR). Two solvent systems were used as eluents: 1) n-butanol–acetic acid–water (4:1:5); 2) alcohol–25% aqueous ammonia (10:1).

The IR spectra of compounds Ia-f (KBr pellets) showed absorptions due to stretching vibrations at 3400 cm^{-1} (OH and NH), 1600-1620 cm^{-1} (C=O), and 1580 cm^{-1} (C=C and C=N of the pyrimidine ring), and absorptions due to deformation vibrations at 1450 cm^{-1} (NH and OH of the pyrimidine ring), 1220-1240 cm^{-1} (C=C), and 750 cm^{-1} (pyrimidine ring CH).

EXPERIMENTAL CHEMISTRY

Infrared spectra were taken on a Perkin-Elmer instrument (Sweden), UV spectra of ethanol solutions on an MPS-5000 spectrophotometer (Japan), $c = 1 \cdot 10^{-3}$ moles/liter.

2-Phenylamino-4-(o-carboxyphenylamino) pyrimidine (Ia). To 4.6 g (0.2 moles) of metallic sodium dissolved in 50 ml of absolute methanol was added 18.6 g (0.2 moles) of aniline and 24.9 g (0.1 moles) of 2-chloro-4-(o-carboxyphenylamino)pyrimidine. The reaction mixture was heated in a sealed tube at 110°C for 6 h, cooled, the precipitated sodium chloride filtered off, the filtrate diluted with water and neutralized with 50% acetic acid to pH 6.0. The precipitate was filtered off, washed with water and ethyl alcohol, and recrystallized from ethanol.

2-Hydrazino-4-(o-carboxyphenylamino)pyrimidine (Ib). A stirred mixture of 24.9 g (0.1 moles) of 2-chloro-4-(o-carboxyphenylamino)pyrimidine and 10 g (0.2 moles) of hydrazine hydrate in 30 ml of methanol was heated under reflux on a water bath for 3 h. The precipitated material was filtered off and recrystallized from 50% aqueous ethanol.

Hydrochloride of 2,4-Di-(o-carboxyphenylamino)-5-bromo-6-methylpyrimidine (Ic). A mixture of 34.2 g (0.1 moles) of 2-chloro-4-(o-carboxyphenylamino)-5-bromo-6-methylpyrimidine

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TABLE 1. o-Carboxyphenylaminopyrimidines Ia-f

Compound	Yield, %	Melting point, °C	Found, %		Empirical formula	Calculated, %		$R_f \cdot 100$ in system		UV spectra, λ_{max} in ethanol, nm
			N	Cl		N	Cl	1	2	
Ia	81	279—80	18.30	—	$C_{17}H_{14}N_4O_2$	18.28	—	41	74	214, 274, 328
Ib	80	329—31	16.88	—	$C_{18}H_{16}N_4O_2$	28.56	—	33	52	216, 242, 319
Ic	60	298—9	11.79	7.55	$C_{18}H_{13}BrN_4O_2 \cdot HCl$	11.68	7.39	62	48	228, 283, 336
Id	84	200	12.83	8.21	$C_{18}H_{14}N_4O_2 \cdot HCl$	13.01	8.23	14	20	284, 348
Ie	76	210	14.30	8.86	$C_{18}H_{13}ClN_4O_2 \cdot HCl$	14.58	9.22	64	52	234, 279, 336
If	80	385	14.16	8.58	$C_{18}H_{16}N_4O_4 \cdot HCl$	15.87	8.84	64	45	232, 280, 326

TABLE 2. Antiinflammatory Properties of the o-Carboxyphenylaminopyrimidines Ia-f

Compound	LD_{50}, mg/kg (intraperitoneally)	% decrease of formalin edema of the paw	Increase in threshold of pain sensitivity in mice, %	Antipyretic action in rats ($\Delta t°$)
Ia	1130	28,5±4.4	127,3±17,6	1,5±0,18
Ib	640	13,4±6.0	—	—
Ic	330	9±3,2	53±7,4	1,9±0,26
Id	460	48±6.0	62±4,6	2,0±0,13
Ie	550	34±4.9	54±7,7	2,3±0,9
If	400	45±3,2	74±6,0	1,3±0,22
Sodium mefenamate	150	30,6±7,8	55,1±5,0	1,5±0,22

and 13.85 g (0.11 moles) of anthranilic acid was heated on an oil bath at 100°C for 2 h. The precipitate formed was filtered off, washed with alcohol, and recrystallized from 50% acetic acid. Compounds Id-f were obtained in the same way from substituted 2-chloro-4-(o-carboxyphenylamino)pyrimidine and anthranilic acid.

EXPERIMENTAL BIOLOGY

A study was made of the acute toxicity, antiinflammatory, analgesic, and antipyretic activity of the 4-(o-carboxyphenylamino)pyrimidines Ia-f. The data obtained are given in Table 2.

Acute toxicity was determined by intraperitoneal injection into white mice of both sexes weighing 20–25 g; antiinflammatory and antipyretic action on rats of both sexes weighing 150–200 g.

Antiinflammatory action of the substances was determined from observations of edema of the rear paw of the rat, induced by the supplantar injection of 2% formalin. The test compounds were injected intraperitoneally as suspensions in starch at a dosage of 1/10 of the LD_{50} 30 min before the injection of formalin. The volume of the paw was measured plethymographically 4 h after the injection of the inflammatory agent.

The antipyretic activity of the compounds was studied in tests on rats with milk fever caused by the injection of boiled skimmed cow's milk heated to 37–40°C (intramuscularly; 1 ml per 100 g of body weight). Compounds Ia-f were injected at the peak of the fever and the antipyretic action monitored over a period of 3 h.

The analgesic activity was studied on white mice weighing 20–25 g by the method described in [7, 8] by determining the threshold of sensitivity of heat. Pyrimidines Ia-f have low toxicity with LD_{50} of 330–1130 mg/kg. The toxicity depends somewhat on chemical structure. The 2-(o-carboxyphenylamino)pyrimidines are more toxic than their analogs with an unsubstituted phenylamino or hydrazino group in the 2 position of the pyrimidine ring. The most toxic compound was Ic — 2,4-di(o-carboxyphenylamino)-5-bromo-6-methylpyrimidine.

Compounds Ia-f possess antiinflammatory properties and suppressed the development of formalin edema of the paw. The most active compounds were the 2,4-di(o-carboxyphenylamino)-pyrimidines Ic-f.

All the compounds also exhibited analgesic properties: The most active was 2-phenylamino-4-(o-carboxyphenylamino)pyrimidine Ia.

These compounds exhibited antipyretic action lowering the body temperature of a rat with milk fever. Most active were the 2,4-di(o-carboxyphenylamino)pyrimidines. In this group of compounds, preparation Ie — 2,4-di(o-carboxyphenylamino)-6-chloropyrimidine had the greatest antipyretic effect.

Thus, compounds Ia-f are less toxic than sodium mefenamate or brufen, and exhibit anti-inflammatory, analgesic, and antipyretic action.

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BROMINE ANALOGS OF QUINOXIDINE, DIOXIDINE, AND AMIDES OF DI-N-OXIDES OF 3-HYDROXYMETHYLQUINOXALINE-2-CARBOXYLIC ACID

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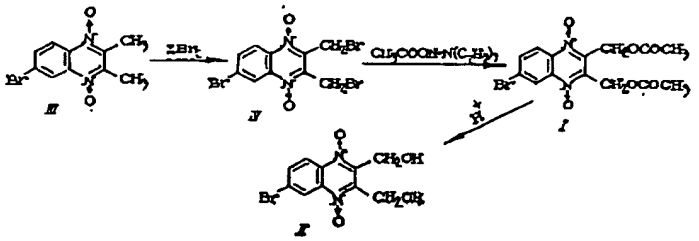
We investigated the synthesis of bromine analogs of the biologically-active quinoxaline derivatives quinoxidine, dioxidine, and amides of di-N-oxides of 3-hydroxymethylquinoxaline-2-carboxylic acid [1-3] in order to study their biological activity.

The bromine analogs of quinoxidine [2,3-bis(acetoxymethyl)-7-bromoquinoxaline-di-N-oxide (I)] and dioxidine [2,3-bis(hydroxymethyl)-7-bromoquinoxaline-di-N-oxide (II)] were synthesized as indicated in the scheme below from 2,3-dimethyl-7(6)-bromoquinoxaline-di-N-oxide (III) by means of the intermediate 2,3-bis(bromomethyl)-7(6)-bromoquinoxaline-di-N-oxide (IV).



Amides of 3-hydroxymethyl-7-bromoquinoxaline-2-carboxylic acid di-N-oxide (XXIIIa-i) were synthesized from 2-carbethoxy-3-methyl-7-bromoquinoxaline-di-N-oxide (V), which was in turn prepared by a known method: the reaction of 5(6)-bromobenzofuroxane (VI) with esters of acetoacetic acid in the presence of various basic reagents [4, 5]. These authors recommended the use of the 7- and 6-bromo isomers of 2-carbalkoxy-3-methylquinoxaline-di-N-oxide

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